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SHORTER ARTICLES AND CORRESPONDENCE

THE BEARING OF THE SELECTION EXPERIMENTS OF CASTLE AND PHILLIPS ON THE VARIABILITY OF GENES

CASTLE and Phillips have recently reviewed the results of six years' work in which they selected for and against "hoodedness" in rats.[1] In "hooded" or "piebald" rats only part of the coat is pigmented; the area of dark (versus white) coat varies greatly in different animals, but tends, in those of medium grade, to cover the head, shoulders and middle of the back, like a hood. Starting with a strain which was probably hybrid, although of unknown ancestry, and selecting during thirteen generations for a larger extent of colored coat ("plus" selection), they succeeded in obtaining animals with a greater and greater area of pigmentation. The average, the mode, and the extremes were raised. Conversely, selection for less pigmentation ("minus" selection) was accompanied by a gradual but decided and continual dimunition in the dark area. "Return" selection also succeeded; that is, plus selection was effective even in a line which was already lighter than the average on account of a previous minus selection, and, *vice versa,* minus selection caused a lightening of a strain that had been made exceptionally dark by a prior plus selection.

Certain crosses proved that more than one factor affecting hoodedness is involved in the difference between the different races. Therefore the production of animals of desired grade by selection may perhaps be explained as a mere sorting out, into different lines of descent, of different combinations of the various factors for hoodedness originally present in the heterozygous ancestors. It is the opinion of Castle and Phillips, however, that this explanation will not suffice to account fully for the continued efficacy of selection in their experiments, and they believe it probable that a factor or factors for hoodedness are undergoing variation of a fluctuating nature.

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[1] Castle and Phillips, "Piebald Rats and Selection, An experimental test of the effectiveness of selection and of the theory of gametic purity in Mendelian crosses." Published by the Carnegie Institution of Washington. See also Castle's "Pure Lines and Selection" in *American Breeders' Magazine,* 1914.

A conclusion so radical and so opposed to previous work should not be accepted, however, as long as it remains at all reasonably possible to use instead an explanation in harmony with the results of Johannsen and other investigators. Johannsen dealt with a character—dimensions of seed—which must beyond any doubt have been partially dependent upon a very great many factors, yet he found that selection had no effect whatever after he had separated the different genotypes from one another. Thus he proved the constancy of a great many genes "at one blow"—namely, of all the genes appreciably concerned in seed size. Of course, if there had been a chance for cross-fertilization in his experiments, he, like Castle, would have obtained a result from selection, but this would have been due to recombination, not variation, of genes. All our evidence points to the conclusion that the vast majority of genes are extremely constant, although they differ somewhat in that very slight amount of variation which they do show. For example, in *Drosophila*, although in the case of most genes not more than one mutation has been found, yet in one case (possibly in two or three cases) a locus has mutated three times, each time in a different way, thus giving rise to a system of multiple allelomorphs containing four members. This gene evidently is more subject to mutation than the others, yet this formation of a series of multiple allelomorphs can not even remotely be compared to fluctuating variability, for the three mutations were all large steps (much smaller could easily have been detected), and they were found only during the examination of some millions of individuals in the rest of which the locus was not observed to mutate at all. Some few genes are known, however, which really do change frequently (*e. g.*, that for "variegated" corn), but these cases are extremely rare; moreover, here the degree and nature of the change are fixed, and also, after the change has once occurred the instability of the gene is lost. Thus, in no known case do the variations of a gene among, let us say, several thousand immediate descendants of the individual possessing it, form a probability curve, as neo-Darwinians might perhaps suppose, nor even are any cases known where genes can undergo frequent changes that may vary at all in kind or amount or occur successively.

Let us then inquire into the probability and adequacy of that explanation of Castle and Phillips's results which does not require the assumption that a gene or genes involved change comparatively frequently and successively, but which assumes a sorting out of numerous factors. It is now pretty generally accepted by Mendelians that the germ plasm of any of the higher organisms contains a large number of genes, which play various rôles in the numberless processes and reactions of development whereby the egg is transformed into the adult individual. The exact nature and intensity of any one characteristic of this adult organism (*e. g.*, hoodedness in rats) is dependent upon the nature of each of the various reactions which were involved in producing this character, and thus dependent upon all the genes (and environmental factors also) involved in any of those reactions. Now, in an ordinary Mendelian cross, all the individuals are usually homozygous and alike in respect to all but one of the pairs of genes that noticeably affect the character concerned. In such a case, then (so far as differences in environmental influences do not obscure the outcome), one obtains the simple Mendelian results derived from the segregation, at reduction, and recombination, at fertilization, of but this one pair of allelomorphs.

The strain of hooded rats, however, was probably a hybrid between two races of rather remote relationship. When two such races are crossed, the individuals often differ in more than one pair of those factors that affect the character studied, especially if the character is such as to be influenced by a relatively large number of genes. It can not be questioned that some characters are thus determined or influenced by a much larger number of developmental reactions than are others, and such characters will therefore vary more in inheritance, since if a difference exists between two individuals in respect to any given gene, these characters are more likely to be affected than others. Gross size, for example, is a character dependent in this way upon an exceptionally large number of genes, for any gene which influences the size of any organ must affect to some extent the total size. In some other cases in which characters are found to be influenced by relatively many genes, the reason for this is not so evident, *e. g.*, in the case of the red flower-color of flax, or the truncated condition of the wing in some races of *Drosophila*. Here the production of the character may be conceived to be dependent upon some reaction that can be easily modified by various means.[2] For our present purpose we must assume that the character "hoodedness" belongs in this class and that the ancestral hooded rats used by Castle and Phillips were the descendants of a cross involving many genes for that character.

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[2] It is conceivable that differences in respect to numerous genes have sometimes arisen even in the case of characters not naturally very easily

The results of such a cross are of course complicated, for the different pairs of allelomorphs generally can undergo recombination at the reduction division of the hybrid, so that in F_2 or subsequent generations as many different genetic types of individuals are formed as there are possible different combinations of those factors wherein the ancestors differed. Not all these genetic types, of course, will fall into different phenotypes, yet generally there will be a large number of overlapping phenotypes among the progeny.

The larger the number of factors in which the two ancestral lines differed, the larger will be the number of different possible combinations of these factors, and accordingly the smaller will be the chance of any individual having one of those particular combinations necessary to a relatively high or a relatively low intensity of the character. In other words, the larger the number of factors (for one character) for which a population is heterogeneous, the more numerous are the possible different grades of intensity of this character among the different individuals, but the fewer will be the individuals which approach the more extreme grades theoretically possible in such a population.[3] Suppose, for example, that two parents differ in five pairs of factors for hoodedness, which are partially dominant[4] to their allelomorphs and summative in their action. Then in F_2 not one

influenced by diverse means, merely because one of the two races had been subjected to a very long and drastic selection, so that any of those rare mutations which affected that character in the desired direction had in this race been preserved. Selection in such a case, however, would have to involve many millions of individuals.

[3] One extreme, *e. g.*, the "plus," will be rather frequent, however, if all the "plus" factors dominate completely. But in the case of the hooded rats we must assume either that dominance is generally incomplete or that in the case of some factors the "minus" allelomorph dominates in the case of others the "plus," since F_1 rats from a cross of the plus by the minus strain are on the average intermediate in type between these two extremes.

[4] It is of course by no means necessary to assume incomplete dominance of the factors. If dominance is complete (in some cases the "minus" factor may dominate, in others the "plus"), the rigor of selection will be diminished, since heterozygous forms can not be distinguished from homozygous. Therefore, although a somewhat greater number of individuals will be found having the limiting values, it will take longer to bring the average up to the limit.

individual in a thousand will have the most extreme dark or light grade of hoodedness possible. However, by selecting the more extreme individuals, and mating them together, a still more extreme grade of hoodedness may be obtained in F_3 (both as to average and limiting values), and the same process may be continued for a good many generations. The number of generations during which effective selection is possible depends on the number of factors concerned, the rigor of selection, and the amount of inbreeding of brother to sister.

In regard to the latter point, since brother and sister are much more apt to be alike in their genetic constitution than are other individuals, offspring from such a mating are more apt to be homozygous and alike, or, we may say, such offspring will tend to be homozygous and alike in a larger number of factors; then, mating two individuals homozygous for these factors together, there will be much less variation and so less opportunity to continue selection among their progeny. In the case of Castle and Phillips's experiments, however, no such attempt at inbreeding was reported. Here, then, the individuals mated together would be more apt to differ genetically, even though they looked alike (thus, one might be AA bb, the other aA bB), and their descendants would therefore present a larger number of different combinations of factors for the selector. Often a greater effect may be eventually produced in this manner than by inbreeding, for a larger number of combinations of factors are thus produced, some of which may be of more extreme type. The effect would usually be slower, however, since such matings tend to keep the strain heterozygous and are often steps backwards. Cross-breeding, then, will help to explain the relatively slow but long-continued and eventually large effect of selection in Castle and Phillips's experiments, although such a result could also be obtained without cross-breeding if the factors were numerous enough.

The "return selections" also are easily explicable on the multiple factor view. Due to the original difference in so many factors, and the fact that cross-breeding diminishes the tendency to homozygosis which selection favors, the rats were presumably heterozygous even after generations of selection. They would not be as heterozygous as before, of course, and, correspondingly, Castle and Phillips did find less variation in the rats after selection. Yet there would still be a good chance for recombination, and an alteration in the race could therefore be produced by further selection or by return selection. As we have seen, this is especially true if certain factors are completely dominant, although dominance is by no means a necessary condition.

As a very simple illustration, let us suppose that the "plus" factors A and B dominate over the "minus" factors "a" and "b," respectively, and each increase the pigmented area to about the same extent. To begin with, two moderately hooded individuals, Aa bb and aa Bb, were mated together. They produced 1aa bb—light-hooded, 1aa Bb and 1Aa bb—both moderate, and 1Aa Bb—dark. We first select for dark; mating the dark rats together, 9 darks, 6 moderates, and 1 light, would be produced (F_2). The average color of the offspring has thus been increased by selection (the limiting color, too, if dominance is incomplete). It can be still further increased in subsequent generations. On the other hand, the color can be made lighter again by a "return selection," for if, instead of mating the F_2 or F_3 darks together, we mate the moderates or mate darks with moderates, many of the matings will give offspring lighter, on the average, than in the preceding generation; *e. g.*, Aa Bb by Aa bb gives 3 dark, 4 moderate, 1 light, as compared with the previous 9 dark, 6 moderate, 1 light. In subsequent generations, the average could be brought still lower.

Let us now see whether there is any experimental evidence in support of the multiple factor explanation of Castle and Phillips's results, aside from the fact that it is adequate and is the only one consistent with other work. One point of evidence we have noted—the variability of the rats continued to decrease as a result of selection in either direction. This we should of course expect on the multiple factor view, for selection gradually tends towards homogeneity in a population, even though it may require a long time to produce complete homogeneity. The second and strongest evidence is from crosses.

The crosses show that one of the factors concerned in differentiating hooded rats from wild rats, which are pigmented all over, or from "Irish" rats, which are almost completely pigmented, is "hypostatic." In other words, a rat having the normal allelomorphs of this factor will always be self-colored, or nearly so; one having the other allelomorphs will always be distinctly hooded, although the amount of the hoodedness varies. "Self," as it happens, is dominant, in this case, over hooded.

Thus, on crossing a hooded to a wild or Irish rat, all the F_1 are self (or nearly so); in F_2 there are three selfs to one hooded, but the hoodeds vary in intensity. The question then is, does this variation (so far as it is not due to "environmental" differences) depend upon what other "epistatic" or "modifying" factors for hoodedness may or may not be present, or is there evidence that it depends instead, or in addition, upon a variability of one or more of the factors for hoodedness? As will be shown below, it can be proved that different combinations of modifying factors do occur in the different hooded indiviuals: this being true, there can be no ground for making the unusual postulate that in this case or in the selection experiments a factor or factors concerned undergo variation.

The proof is that when light hooded rats from the minus strain are crossed to wild or Irish rats the hooded rats in F_2 vary much more than did the original strain of hooded rats and average much darker. Obviously, the P_1 hooded rats differed from the wild or Irish in a number of modifiers as well as in the hypostatic factor; moreover, as we should have expected, this difference consisted chiefly in the fact that the wild or Irish rats contained "plus" allelomorphs in place of some of the "minus" modifiers present in the P_1 strain that had undergone minus selection. Thus the F_2 hooded rats, containing various combinations of these modifying factors wherein the two strains differed, varied much more than did the parental strain of hooded rats, and were on the average much darker.

In order to escape this conclusion that modifying factors were involved, Castle and Phillips at first postulated that the reason that the F_2 hooded were darker than the original "minus" strain was because the factor for hooded had in many cases become contaminated by its allelomorph (the factor for self) in the F_1 rats. This is violating one of the most fundamental principles of genetics—the non-mixing of factors—in order to support a violation of another fundamental principle—the constancy of factors. The refutation of their supposition came unexpectedly soon. It would be expected, on the view of multiple factors, that the wild or Irish rats (containing the allelomorph for self in place of the hypostatic factor for hooded) would not possess as many "minus" modifiers as the hooded strain which had been specially selected to contain as many of these as possible; neither would these "self" rats contain as many "plus" modifiers as the hooded strain which had undergone plus selection (and which so contained nearly all of the plus modifiers originally present in *either* the self or the hooded ancestors). Thus it was to be expected that, just as a cross of self with the minus race gave F_2 hooded rats darker than the original minus strain, so a cross of wild or Irish rats with hoodeds resulting from the plus selection would give F_2 hooded rats *lighter* than those of the plus strain. This result was actually obtained. It was fatal to the idea that the difference between the P_1 strain of hooded rats and the F_2 hoodeds was due to contamination of the allelomorph for hooded with that for self, since such contamination should have resulted in F_2 hooded rats *darker* than those of P_1, not lighter. For wild and Irish rats are both much more extensively pigmented than hoodeds even of the plus strain.

The change in hoodedness from P_1 to F_2 was therefore due to recombinations of the modifying factors wherein the two strains differed. That many such modifiers were concerned is indicated by the evenly distributed variability of the F_2 hoodeds and the fact that very few were as extreme as the hooded grandparents. The same fact is brought out in a cross of the minus with the plus race; here no clear-cut ratios were obtainable, the classification into different genotypes being rendered impossible by the multiplicity of factors (no one of which was hypostatic as in the other crosses). Of course, this knowledge of so many factors being concerned in the crosses helps our interpretation of the selection results decidedly, for the more numerous are the factors concerned, the longer would it be possible to continue an effective selection on the progeny of the hybrids, and the original hooded rats of the selection experiments were admittedly in all likelihood descended from just such hybrids. The exact number and effect of the different factors can not be determined from Castle and Phillip's data, since to do this very special crosses must be made and individual pedigrees kept. Selection experiments can be of little value so long as there are factors for which the individuals may be heterozygous, unless these factors can be accurately followed in inheritance.

Of course, it is quite possible that in the course of these long-continued experiments mutations affecting the hoodedness occasionally happened to arise, especially since it seems likely that this character is dependent upon an unusually large number of genes, for then, as a matter of mere chance, any mutation which occurred would be more likely to affect it than it would be to affect most characters. It is interesting to note that one such mutation, of a very marked and unquestionable character, was in fact observed. The mutant factor proved to be a strong "plus" modifier, which was almost completely dominant, and itself showed no contamination or variation, so far as could be determined. It arose, as it happened, in the plus strain. A part of the effectiveness of selection may therefore have been due to the occurrence and sorting out of such occasional mutations, but there is no way of telling how many of these took place, or *any* need for assuming them at all in explaining the result. These rare mutations, however, would form a very different phenomenon from such fluctuating or frequent and progressive variation of a gene or genes concerned as Castle postulates. Although the academic possibility of variation of the latter type can not be denied, there is no experimental evidence which can be used to support it, and there is good evidence against it in many individual cases.

It is difficult to believe that this suggestion of Castle and Phillips was not made in a spirit of mysticism, when we consider also their suggestion that the genes may undergo contamination, and especially when we consider the following passage, with which their paper concludes:

> It seems to us quite improbable that the plus mutation could have arisen in the minus selection series. We believe that the repeated selection which was practised had something to do with inducing this change in the plus direction. If one can increase at will the "modifiers" which make the pigmentation more extensive, it does not seem strange that after a time a readjustment should occur within the cell which should incorporate modifiers in that part of the cell which is responsible for the unit-character behavior of the hooded pattern. This would amount to a quantitative change in the unit-character for hooded pigmentation.

To thus suppose that independent genes *fuse* or induce changes in one another, merely because they happen to produce similar *end effects* upon the organism, and in spite of the fact that they usually lie in different chromosomes and are apt to differ from each other as much as do other genes, is utterly teleological.

A paper by A. L. and A. C. Hagedoorn criticizing Castle's work and conclusions, appeared at the same time as the paper of

Castle and Phillips.[5] The Hagedoorns champion the multiple factor hypothesis as an explanation of Castle's results, and also cite certain rather inconclusive experiments of their own to support this point of view. They err, however, in supposing that the factors concerned must be incompletely dominant; as we have seen, this is not a necessary assumption, if we admit that in the case of some modifiers the "minus" allelomorph dominates, in others the "plus." They also err in denying the possibility, on the multiple factor view, of successful "return selection," if inbreeding be strictly followed. In fact they offer this as a test of their point of view. As we have seen, "return selection" would be possible in some cases, even if the animals were inbred; and in Castle and Phillips's experiments, where inbreeding was not followed, "return selection" was certainly very effective.

Finally, papers have recently appeared by MacDowell,[6] in which he gives evidence that certain other cases of inheritance (*e. g.*, head size in rabbits), formerly considered by Castle to support the idea of genic variation and contamination, are probably best interpreted on the view of multiple factors instead. His evidence consists in the fact that the characters concerned are somewhat more variable in the offspring of back-crosses than in F_1, as we should expect on the basis of recombination of multiple factors, but which he believes could not plausibly be explained otherwise.

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[5] A. L. & A. C. Haagedorn, "Studies on Variation and Selection," *Zeit. f. ind. Abst. u. Verab.*, 1914.

[6] E. C. MacDowell, "Multiple Factors in Mendelian Inheritance," *Jour. Exp. Zool.*, 1914, and Carnegie Inst. of Wash., 1914.